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Human Infection with Vibrio Fetus

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Vibrio fetus, a slowly growing, microaerophilic, Gram-negative rod which causes infectious abortion in cattle, occasionally induces disease in man. Since persons receiving immunosuppressive agents are among those most susceptible to this infection, recognition of the disease may become increasingly important as transplantation operations increase. Vibrio infections may produce a spectrum of acute and chronic illnesses or may be asymptomatic. Vibriosis may develop at any age but it seems most devastating in the very young or in older debilitated patients. The organism is sensitive to many common antibiotics but has a propensity to produce chronic relapsing illness if treatment is not continued long enough. The method of transmission of the agent is uncertain. Fewer than 100 cases of human vibriosis have been reported, perhaps because of fastidious growth requirements and the initial ease of antibiotic suppression; however, the true incidence of human infection is likely much higher.

VIBRIO FETUS, long known as a causative agent of infectious abortion in cattle, was first recognized to produce human disease in 1947.[1] Since that time, more than 75 cases of local and systemic infection by this organism have been documented in residents from several regions in the United States as well as from abroad.[2-25] Two cases have been reported previously from California.[17,24]

Small infants and elderly adults, as well as patients with chronic debilitating diseases or those receiving immunosuppressive agents, are particularly susceptible to vibriosis. Hence, infections by this organism, like those due to pneumocystis caranii, cytomegalovirus, fungi such as Candida, mucor, and aspergillus, and other "opportunistic invaders" may be expected to become increasingly important wtih the development of transplantation centers and the expanding use of immunosuppressive therapy.

The protean nature of the clinical manifestations of human vibriosis, the propensity for the causative organism to produce a relapsing illness, and the fastidious growth requirements for successful culture of vibrio fetus all suggest that this agent may come to rank among the most troublesome of the opportunistic infections. The recent

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observation of a patient with vibriosis cared for at the Los Angeles County-Martin Luther King, Jr., General Hospital and identification of four additional cases by the laboratories at Los Angeles County-University of Southern California Medical Center emphasize these difficulties and prompt the present report.

Reports of Cases

CASE 1. A 67-year-old black male janitor was admitted to hospital 29 March 1972 because of sudden onset of chills, fever and confusion a few hours earlier upon awakening. The patient's wife said that he was a long-standing alcoholic and that he had retired early the previous evening in his usual state of inebriation but without complaining of feeling ill. Past history was notable for a prolonged febrile illness at age 14 diagnosed as rheumatic fever. Seven years before admission he had undergone bronchoscopy and scalene node biopsy because of right middle lobe atelectasis, but no abnormalities were discerned. One year later he was seen at another hospital because of "stress erythrocytosis" and examination showed a red blood cell mass of 35 ml per kg. An intravenous pyelogram showed no abnormality. Four years before admission, peritoneoscopy and liver biopsy showed Laennec's cirrhosis. The patient had resided in the Watts area of Los Angeles since 1943. However, as a youth he lived in Colorado where he frequently worked with cattle. After 1936, he had no significant contact with animals except for a small dog, with which he had slept during the three years before the present admission.

On physical examination the patient appeared acutely ill and emaciated. He had shaking chills and body temperature of 40°C (104°F). Blood pressure was 130/82 mm of mercury and the pulse rate 132. Ecchymosis was present on both forearms. Results of examination of the head, eyes, ears, nose and throat were within normal limits. The neck resisted motion in all planes, but there were no lower extremity meningeal signs. No lymphadenopathy was detected. Fine inspiratory rales were heard over the left lower lung fields posteriorly. The cardiac rhythm was regular; a diffuse apical thrill was accompanied by a Grade III/VI holosystolic murmur radiating into the axilla. The abdomen was soft and the liver edge was percussed 5 cm below the right costal margin.

Leukocytes numbered 23,000 per cu mm with 85 polymorphonuclear cells, 1 band form, and 14 lymphocytes. The hemoglobin was 10.9 grams per 100 ml of blood and the prothrombin time was 25 percent of normal. Blood sugar was 137 mg per 100 ml. The determinations of blood urea nitrogen, serum transaminase (SGOT), sodium, potassium, chloride and carbon dioxide were within normal limits, and a VDRL test was negative. Creatinine was 1.4 mg per 100 ml. The amylase was elevated to 350 international units. Serum electrophoresis showed albumin of 3.1, alpha-1 globulin 0.3, alpha-2 globulin 0.7, beta-globulin 0.9, and gamma-globulin 1.3 grams per 100 ml. A bromsulphalein test indicated only 6 percent retention at 45 minutes. Urinalysis showed a trace of protein. Cardiomegaly was observed on an x-ray film of the chest, and an electrocardiogram showed incomplete right bundle branch block.

Initial attempts to secure spinal fluid and sputum specimens were unsuccessful, and after specimens of blood and urine for cultures had been obtained, both cephalosporin and kanamycin were administered. The body temperature gradually decreased and the patient improved steadily over the ensuing 48 hours. By the fourth hospital day he was afebrile, alert, and oriented. The number of leukocytes had fallen to 10,600 per cu mm. An x-ray film on the fifth hospital day showed a left lower lobe infiltrate and pleural effusion. On thoracentesis 1,100 ml of clear yellow fluid was withdrawn; it had protein content of 1.3 grams per 100 ml and 10 leukocytes per cu mm. No organisms were cultured from the fluid and no malignant cells were identified.

By the tenth hospital day, the patient appeared to have completely recovered from the acute illness, and antibiotics were discontinued. However, on the 13th hospital day the temperature again rose to 39°C (102°F), the patient became disoriented and restless and the white blood cell count increased to 15,000 per cu mm. An x-ray film showed reaccumulation of the left pleural effusion and an additional small effusion on the right. On the same day, the laboratory reported that a very slowly-growing, microaerophilic, Gram-negative rod had been recovered from the initial blood cultures. Urine cultures were negative. Blood cultures were again obtained and ampicillin was administered intramuscularly. Again the patient quickly responded to parenteral antibiotics and, after four days, was able to take oral medication which was continued for the

following two months without evidence of any relapse.

Organisms isolated from cultures of blood at the time of admission and on the thirteenth day were subsequently confirmed as vibrio fetus by the Los Angeles County-University of Southern California Bacteriology Department and by the State of California Department of Public Health. Serum from blood specimens obtained three and a half weeks after onset of the acute illness revealed a vibrio fetus hemagglutination titer of 160 against St. Luke's strain.*

Following are summaries of four additional cases at LA County-USC Medical Center in which positive cultures for vibrio fetus were obtained.

CASE 2. A 30-year-old Hawaiian-Chinese man was admitted 29 May 1971 with cellulitis of the right leg, jaundice and diffuse toxic goiter. Also noted on examination were temperature of 40°C (104°F), rapid atrial fibrillation, hepatomegaly, and congestive heart failure. The hemoglobin was 10.9 grams per 100 ml of blood, and leukocytes numbered 17,900 per cu mm. Tests of thyroid function showed pronounced increase. Despite treatment with sedatives, digitalis, diuretics, and cephalosporin, the patient died on the second hospital day. Vibrio fetus was grown in five days from several blood cultures obtained shortly after admission.

CASE 3. A 20-year-old schizophrenic man who had been admitted previously several times with drug overdose, entered the hospital 26 March 1968 with four days of left lower quadrant crampy pain, bloody diarrhea, and rectal prolapse. Examination showed rectal temperature of 40.6°C, a soft, somewhat tender abdomen with absent bowel sounds and mild rebound tenderness. Hemoglobin content was 17.7 grams per 100 ml of blood and leukocytes numbered 15,500 per cu mm. Abdominal x-ray films showed ileus. The patient was treated with penicillin and streptomycin and the temperature returned to normal in 48 hours. Blood cultures obtained early in the hospital course were reported positive for vibrio fetus after five to twenty-three days of incubation. After nine days of antibiotic treatment in the hospital the patient was discharged and did not return for follow-up examination.

CASE 4. A 21-year-old man was admitted 29 July 1972 with fever, chills and arthralgias of eight hours' duration. Examination revealed fever (38.4°C) and erythema nodosum involving the lower extremities. There were 11,700 leukocytes per cu mm with 59 neutrophils and 26 lymphocytes. Culture of material from the throat grew H. influenza and D. pneumonia. Blood cultures were initially thought to be positive for staphylococcus and the patient was treated with methicillin. He was discharged, well, after ten days. A week later he was readmitted, the organisms in the blood having been further identified as vibrio fetus. At this time, he was asymptomatic. Repeat blood cultures were obtained as well as cultures of cerebrospinal fluid, urine, and sputum. One of ten blood cultures was positive for vibrio fetus. He was treated with tetracycline and streptomycin for six weeks and was still asymptomatic on follow-up examination several weeks later.

CASE 5. A 65-year-old man, a chronic alcoholic, was admitted 19 October 1971 with a ten-day history of diarrhea. On examination he had fever (40°C), rales at the base of the right lung, and atrial fibrillation. Laboratory studies showed elevated blood sugar and changes consistent with chronic liver disease. Cultures of cerebrospinal fluid and urine were negative while the stool was positive for E. coli. Blood cultures showed no growth for two weeks; then vibrio fetus was identified. Administration of antibiotics was begun soon after admission, and at the request of his family, the patient was transferred to another hospital—this before the growth of the organism on the culture. He could not be located on attempts at follow-up.

Discussion

Vibrio fetus was first identified as a disease agent in cattle early in this century and subsequently was recognized as a venereal infection transmitted by the asymptomatic bull. The organism remains indefinitely in the testes and can be cultured from the prepuce and semen of infected animals. It is transmitted to the female during copulation and also through artificial insemination. Although insignificant vaginal lesions are apparent in infected cows, the organism attacks the placenta, causing necrosis and suppuration of the fetal membranes resulting in abortion.[2] In this country, vibrio has come to replace brucellosis as the most common cause of abortion in cattle. More frequently than abortion, however, vibrio causes infertility in heifers.[26] The organism has also been isolated from sheep, but the ram is

*The hemagglutination titer was obtained by Dr. B. Bokkenheuser,[28] St. Lukes Hospital Center, New York.

apparently not involved in sexual transmission of the disease and vibrio is part of the normal intestinal flora in this species. Hence, food and contaminated water are suspected as the source of infection in sheep, as well as in other afflicted species, including goats, pigs, cats, dogs, hamsters, guinea pigs, antelopes, chickens, turkeys and humans.

It has been suggested that sheep are natural carriers for vibriosis and harbor the organisms in the gallbladder. The agent has also been grown from the gallbladder in one case of human infection[20] but the significance of this observation remains uncertain. In this regard, differences in strains may be critical. Innoculation of sheep and cattle with vibrio fetalis variants intestinalis and venerealis results in recovery of intestinalis but not venerealis from both sheep and cattle gallbladders.[25] Significantly, vibrio fetus variant venerealis is the principal agent causing abortion in cattle. However, based on biochemical and serological relationships, organisms from humans have identical characteristics to those of vibrio fetus variant intestinalis, the agent regularly causing abortion in sheep but only occasionally the offender in cattle.[26]

In early laboratory cultures, vibrio appears as a short, comma-shaped, flagellated, Gram-negative rod which becomes spirillar when the cultures are older. The organism is microaerophilic, motile, and non-carbohydrate-fermenting. Cultures are catalase-positive and produce hydrogen disulfide.

In many instances, vibrio can readily be cultured and identified under standard laboratory conditions. Frequently, however, growth is very slow, suggesting an as yet unidentified limiting requirement of the media. Variables which appear to influence the success of cultures include: (1) the size of the innoculum, (2) the precise composition of the media, including the type of blood employed in blood agar plates, and (3) incubation conditions (for example, vibrio grows poorly at 42° in thioglycolate, but well on bovine blood agar at this temperature). It is apparent that very slowly growing cultures of organisms, such as were found in the case presented, would often be discarded prematurely as "negative."

While there is no unmistakable clinical pattern characteristic of human vibriosis, the disease uniformly presents as a febrile infection, usually with shaking chills. Additional manifestations have included dysentery,[17] septic joint,[5,9] endocarditis,[8,14] meningitis,[7] pericarditis,[11] lung abscess,[25] and both upper and lower motor neuron paralysis. In patients with endocarditis, the organisms seem to have a propensity for the aortic valve, although infections of the mitral and tricuspid valves have also been reported.[14] The clinical observations in the present case are consistent with endocarditis of the mitral valve although the heart murmur did not change during hospitalization and peripheral manifestations of endocarditis were absent. Occasionally, the organism produces both deep and superficial thrombophlebitis (even at the sites of venipuncture), which early raised the question of vascular tropism.[2,25]

Since the diagnosis of infection with vibrio may be elusive, repeated cultures from a variety of sources are most likely to yield positive results. However, the organism is seldom cultured from two sources simultaneously. While blood cultures are the most common source of identification, the organism has also been cultured from pericardial fluid,[11] cerebrospinal fluid,[24] brain tissue, placenta, synovial fluid, skin pustules,[13] urine[19] and, rarely, from sources of mixed flora such as the vagina or from milk. Interestingly, no positive stool culture has yet been reported in humans.

In humans the organism is reputed to infect primarily the very young or debilitated older patients, particularly those having diseases which have led to treatment with corticosteroids or immunosuppressive agents. Underlying conditions have included lymphosarcoma, chronic lymphatic leukemia, agammaglobulinemia, cirrhosis, diabetes, chronic alcoholism, and brucellosis.[25,27] Infections have not yet been reported in patients undergoing organ transplantation but they would seem to be a likely susceptible group. Only rarely have cultures been obtained from previously healthy persons, but among patients in whom this did occur were a 45-year-old man with acute dysentery,[17] a laboratory technician with skin pustules,[5] a produce worker,[13] and a 74-year-old woman in whom the agent was found in the common bile duct at the time of cholecystectomy.[20] Occasionally, positive cultures have also been obtained from the mouth and vagina of asymptomatic women during pregnancy, and in neonates.[18] The organism has been cultured frequently from women who have aborted,[3,11,12,18,19] but also from women who have carried an infant successfully to term.[19] In infants, the organism has been found primarily in either blood or cerebrospinal fluid. Two cases have been reported in children with sickle cell anemia.[27] In nine of the total of 71

cases collected by Bokkenheuser,[19] the disease occurred during the perinatal period. Three of the nine infected infants were premature and died. Six were born at term without defects; of these, five survived. Diarrhea and meningitis are the predominant features of all reported neonatal cases.

In the epidemiology of human infections, the importance of animal contact has remained uncertain. In the present case, the only known animal contact was with a small dog; attempts to grow the organism from this animal were unsuccessful. In the series collected by Bokkenheuser, one third of the patients had recent contact with animals or animal products, one third denied such exposure, and in the remainder the history was uncertain. Hence, the source of most human infection remains speculative. Among the possibilities are, of course, direct contact with either infected animals or laboratory cultures, sexual contacts (with the possibility of a dormant state in the testis), and exposure to contaminated water or milk with subsequent infection.[4,12,27] It has also been postulated that vibriosis may be contracted through eating contaminated food, such as raw liver.[27] Placental transfer of the organism or exposure at the time of delivery[18] represents a potential source of infection and it has been suggested that the organism can be contracted *in utero*.[19]

An unusual characteristic of vibrio infections in humans is the chronic nature of the disease; bacteremia of long duration has frequently been reported[2,25] with a striking tendency toward relapse during the weeks or months following discontinuation of initial therapy.[19] This is well illustrated in the present case, relapse occurring after a full ten days of treatment with antibiotics to which the organism was sensitive. In addition to endocarditis or abscess formation, possible mechanisms for such relapse might include the development of *in vivo* resistance, or the appearance of "L forms." The available data do not permit adequate assessment of such alternatives.

Although spontaneous recovery from human vibriosis has been reported,[27] more frequently the course of the illness is chronic or relapsing and requires sustained antibiotic therapy. Fortunately, the agent appears sensitive to most common antibiotics, including tetracycline,[4,27] penicillin,[3,6,19] chloramphenicol,[9] sulfa drugs,[10] erythromycin, colistin, cephalosporin, kanamycin and streptomycin.[19] Only occasional resistance to penicillin and tetracycline has been reported.[19] Characteristically, the present patient responded initially to a combination of cephalosporin and kanamycin but, after relapse, responded equally well to treatment with ampicillin. Experience to date suggests that once a clinical response has been obtained to an appropriate antibiotic, therapy should be continued for a prolonged period (at least four weeks) to avoid the possibility of relapse. Even after such prolonged therapy it would seem advisable that, once antibiotics have been discontinued, the patient should be kept under close observation for any evidence of recurrence of the disease.

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